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(54) Title: METHODS OF TREATMENT USING BENZOXAZINONES AS PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR GAMMA MODULATORS

(57) Abstract: The invention is directed to methods of treatment using benzoxazinones as peroxisome proliferator activated receptor gamma (PPARγ) agonists or antagonists.

METHODS OF TREATMENT USING BENZOXAZINONES AS PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR GAMMA MODULATORS

Cross Reference to Related Applications

This application claims priority from U.S. Serial No. 60/203,861, filed May 12, 2000.

Field of the Invention

This invention relates to methods of using benzoxazinones for the treatment of Non-Insulin Dependant Diabetes Mellitus (NIDDM) and complications thereof and disorders related to lipid metabolism and energy homeostasis such as obesity. More particularly, the compounds act through the Peroxisome Proliferator Activated Receptor gamma (PPARγ).

Background of the Invention

Diabetes is a disease caused by multiple factors and characterized by hyperglycemia which may be associated with increased and premature mortality due to an increased risk for microvascular and macrovascular diseases such as nephropathy, neuropathy, retinopathy, atherosclerosis, polycystic ovary syndrome (PCOS), hypertension, ischemia, stroke, and heart disease. Type I diabetes (IDDM) results from genetic deficiency of insulin, the hormone regulating glucose metabolism. Type II diabetes is known as non-insulin dependent diabetes mellitus (NIDDM), and is due to a profound resistance to insulin regulatory effect on glucose and lipid metabolism in the main insulin-sensitive

tissues, i.e., muscle, liver and adipose tissue. This insulin resistance or reduced insulin sensitivity results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue as well as glucose production and secretion in liver. Many Type II diabetics are also obese, and obesity is believed to cause and/or exacerbate many health and social problems such as coronary heart disease, stroke, obstructive sleep apnoea, gout, hyperlipidemia, osteoarthritis, reduced fertility, and impaired psychosocial function.

A class of compounds, thiazolidinediones (glitazones), have been suggested to be capable of ameliorating many symptoms of NIDDM by binding to the peroxisome proliferator activated receptor (PPAR) family of receptors. They increase insulin sensitivity in muscle, liver and adipose tissue in several animal models of NIDDM resulting in correction of the elevated plasma levels of glucose, triglycerides and nonesterified free fatty acids without any occurrence of hypoglycemia. However, undesirable effects have occurred in animal and/or human studies including cardiac hypertrophy, hemadilution and liver toxicity.

Most PPARγ agonists currently in development have thiazolidinedione ring as their common chemical structure. PPARγ agonists have been demonstrated to be extremely useful for the treatment of NIDDM and other disorders involving insulin resistance. Recently, troglitazone, rosiglitazone, and pioglitazone have been approved for treatment of type II diabetes. There is also indication that benzimidazole-containing thiazolidinedione

derivatives may be used to treat irritable bowel disorder (IBD), inflammation, and cataract (JP 10195057).

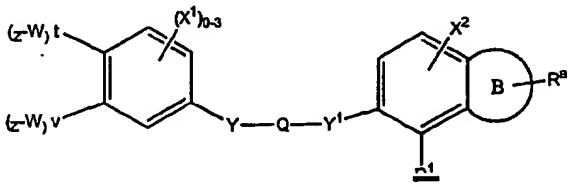
JP 09012576 (Yoshitake et al.) discloses benzothiazine derivatives stated as useful therapeutic agents for circulatory system disease and glaucoma.

JP 09012575 (Hiroaki et al.) discloses benzoxazine and benzothiazine derivatives stated to be useful as prophylactic drugs and/or therapeutic drugs in hyperlipemia, hyperglycemia, obesity, diseases attributable to sugar tolerance insufficiency, hypertension, osteoporosis, cachexia, and complications of diabetes such as retinopathy, nephrosis, neuropathy, cataract, coronary artery disease and arteriosclerosis.

WO 99/20614 (Lohray et al.) discloses ß-aryl-α-oxysubstituted alkylcarboxylic acids stated as antiobesity and hypocholesterolemic compounds which may have agonist activity against PPARα and/or PPARγ, and optionally inhibit HMG CoA reductase.

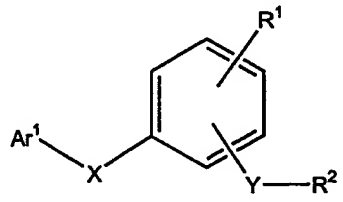
WO 97/17333 (Frechette et al.) and U.S. Patent Nos. 5,696,117 and 5,854,242 to Frechette et al. disclose benzoxazine and pyrido-oxazine compounds including compounds of Formula I, all of which have a moiety of a fused phenyl or fused pyridyl, pharmaceutical compositions containing the compounds, and methods for their production and their use in treating bacterial infections.

U.S. Patent No. 5,859,051 to Adams et al. discloses the following acetylphenols,



wherein substituents are as described in the reference, which are stated to be useful as antiobesity and antidiabetic compounds lacking the thiazolidinedione moiety.

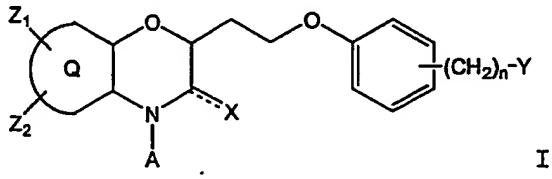
WO 99/38845 (De La Brouse-Elwood et al.) discloses the following compounds,



wherein substituents are as described in the reference, which are stated to modulate the PPARγ receptor and are stated as useful in the diagnosis and treatment of type II diabetes (and complications thereof) and inflammatory disorders.

Summary of the Invention

The present invention is directed to a method of treating a subject suffering from a condition associated with Peroxisome Proliferator Activated Receptor gamma activity, which comprises administering to said subject an effective amount of a compound of Formula I,



I

or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, ester, prodrug form, or a pharmaceutically acceptable salt thereof, wherein

Q is a fused phenyl or fused pyridyl moiety;

Z_1 is hydrogen, halogen, $COOR_1$, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl;

Z_2 is hydrogen or a halogen;

X is hydrogen or oxygen;

A is C_1-C_6 alkyl, C_1-C_6 alkylaryl or C_1-C_6 alkylheterocyclyl

wherein said aryl is biphenyl, naphthyl or phenyl; and said heterocyclyl is a 5- or 6-membered saturated or unsaturated heterocyclic group containing 1-4 nitrogen atoms, an oxygen or sulfur atom;

wherein said aryl or heterocyclyl group is optionally substituted with C_1-C_6 alkyl, benzyl, oxybenzyl, phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro, amino, carboxyl, carbo(C_1-C_6)alkoxy, or methylsulfonylamino;

n is an integer from 0-3; and

Y is selected from

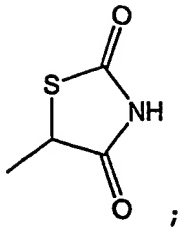
(a) NHR_1R_2, $N^+R_1R_2R_3$;

(b) $NHC(NR_4)NR_5$;

(c) CO_2H, CHO;

(d) $CH(R_6)COOH$, $CH(R_6)COOCH_3$, $CH=CHR_7$, $CH=C(COOH)_2$;

(e) a moiety of the formula



;

(f) 5-tetrazolyl,

wherein

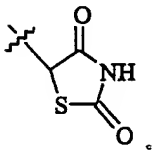
R_1, R_2 and R_3 are independently hydrogen, C_1-C_6 alkyl, or t-butoxycarbonyl;

R_4 and R_5 are independently t-butoxycarbonyl or hydrogen, or R_4 and R_5 may be joined together to form an imidazoline, imidazolyl or pyrimidine ring;

R_6 is hydrogen, hydroxy, or halogen; and

R_7 is CO_2H or $C(O)NH(CH_2)_pOH$ wherein p is an integer from 1-4.

Illustrative of the invention is a method of treating a subject suffering from a condition associated with Peroxisome Proliferator Activated Receptor gamma activity, which comprises administering to said subject an effective amount of a compound of Formula I, or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, ester, prodrug form, or a pharmaceutically acceptable salt thereof, wherein A is C_1-C_6 alkylheterocyclyl when X is hydrogen and Y is



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Also illustrating the invention is a method of treating a subject suffering from a condition associated with Peroxisome Proliferator Activated Receptor gamma activity, which comprises administering to said subject a

pharmaceutical composition comprising an effective amount of a compound of Formula I and a pharmaceutically acceptable carrier.

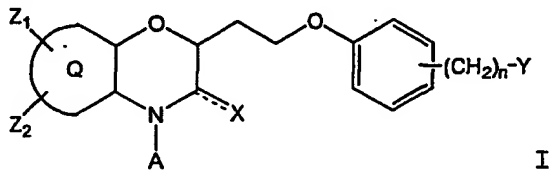
Further illustrating the invention is a method of treating a subject suffering from a condition associated with Peroxisome Proliferator Activated Receptor gamma activity, which comprises administering to said subject an effective amount of a compound of Formula I, or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, ester, prodrug form, or a pharmaceutically acceptable salt thereof, wherein said condition is selected from NIDDM, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis polycystic ovary syndrome, hypertension, ischemia, stroke, heart disease, irritable bowel disorder, inflammation, and cataract.

Also included in the invention is a method of inhibiting in a subject the onset of a condition associated with Peroxisome Proliferator Activated Receptor gamma activity, which comprises administering to said subject an effective amount of a compound of Formula I, or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, ester, prodrug form, or a pharmaceutically acceptable salt thereof.

Further included in the invention is a process for making a pharmaceutical composition comprising mixing any of the compounds of Formula I and a pharmaceutically acceptable carrier.

Detailed Description of the Invention

The present invention provides a method of treating a subject suffering from a condition associated with Peroxisome Proliferator Activated Receptor gamma activity, which comprises administering to said subject an effective amount of a compound of Formula I,



I

or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, ester, prodrug form, or a pharmaceutically acceptable salt thereof, wherein

Q is a fused phenyl or fused pyridyl moiety;

Z_1 is hydrogen, halogen, $COOR_1$, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl;

Z_2 is hydrogen or a halogen;

X is hydrogen or oxygen;

A is C_1-C_6 alkyl, C_1-C_6 alkylaryl or C_1-C_6 alkylheterocyclyl

wherein said aryl is biphenyl, naphthyl or phenyl; and
said heterocyclyl is a 5- or 6-membered saturated or unsaturated heterocyclic group containing 1-4 nitrogen atoms, an oxygen or sulfur atom;
wherein said aryl or heterocyclyl group is optionally substituted with C_1-C_6 alkyl, benzyl, oxybenzyl, phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro, amino, carboxyl, carbo(C_1-C_6)alkoxy, or methylsulfonylamino;

n is an integer from 0-3; and

Y is selected from

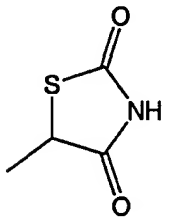
(a) NHR_1R_2, $N^+R_1R_2R_3$;

(b) $NHC(NR_4)NR_5$;

(c) CO_2H, CHO;

(d) $CH(R_6)COOH$, $CH(R_6)COOCH_3$, $CH=CHR_7$, $CH=C(COOH)_2$;

(e) a moiety of the formula



;

(f) 5-tetrazolyl,

wherein

R_1, R_2 and R_3 are independently hydrogen, C_1-C_6 alkyl, or t-butoxycarbonyl;

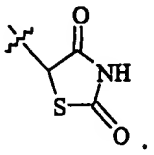
R_4 and R_5 are independently t-butoxycarbonyl or hydrogen, or R_4 and R_5 may be joined together to form an imidazoline, imidazolyl or pyrimidine ring;

R_6 is hydrogen, hydroxy, or halogen; and

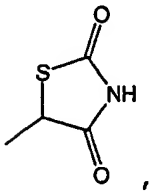
R_7 is CO_2H or $C(O)NH(CH_2)_pOH$ wherein p is an integer from 1-4.

Particularly, the subject is a human and the condition is a disorder in glucose or lipid metabolism. More particularly the condition is reduced insulin sensitivity such as NIDDM and obesity.

Particularly X is oxygen. More particularly R_6 is hydrogen or halogen when n is 1. Still More particularly A is C_1-C_6 alkylheterocyclyl when X is hydrogen and Y is



Another embodiment of the present invention is a method of treating a subject using an effective amount of a compound of Formula I wherein Y is selected from CO_2H, CHO, $CH(R_6)COOH$, $CH(R_6)COOCH_3$, $CH=CHR_7$, $CH=C(COOH)_2$, a moiety of the formula



and 5-tetrazolyl, wherein R_6 and R_7 are as described above.

The present invention also provides a method of inhibiting in a subject the onset of a condition associated with Peroxisome Proliferator Activated Receptor gamma activity, which comprises administering to the subject a prophylactically effective dose of a compound of Formula I,
or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, ester, prodrug form, or a pharmaceutically acceptable salt thereof, wherein

Q is a fused phenyl or fused pyridyl moiety;

Z_1 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl;

Z_2 is hydrogen or a halogen;

X is hydrogen or oxygen;

A is C_1-C_6 alkyl, C_1-C_6 alkylaryl or C_1-C_6 alkylheterocyclyl

wherein said aryl is biphenyl, naphthyl or phenyl; and said heterocyclyl is a 5- or 6-membered saturated or unsaturated heterocyclic group containing 1-4 nitrogen atoms, an oxygen or sulfur atom;

wherein said aryl or heterocyclyl group is optionally substituted with C_1-C_6 alkyl, benzyl, oxybenzyl, phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro, amino, carboxyl, carbo(C_1-C_6)alkoxy, or methylsulfonylamino;

n is an integer from 0-3; and

Y is selected from

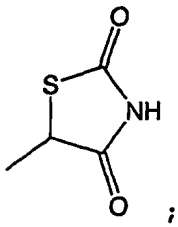
(a) NHR_1R_2, $N^+R_1R_2R_3$;

(b) $NHC(NR_4)NR_5$;

(c) CO_2H, CHO;

(d) $CH(R_6)COOH$, $CH(R_6)COOCH_3$, $CH=CHR_7$, $CH=C(COOH)_2$;

(e) a moiety of the formula



;

(f) 5-tetrazolyl,

wherein

R_1, R_2 and R_3 are independently hydrogen, C_1-C_6 alkyl, or t-butoxycarbonyl;

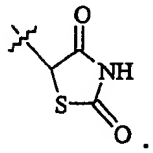
R_4 and R_5 are independently t-butoxycarbonyl or hydrogen, or R_4 and R_5 may be joined together to form an imidazoline, imidazolyl or pyrimidine ring;

R_6 is hydrogen, hydroxy, or halogen; and

R_7 is CO_2H or $C(O)NH(CH_2)_pOH$ wherein p is an integer from 1-4.

Particularly, the subject is a human and the condition is a disorder in glucose or lipid metabolism such as NIDDM and obesity.

More particularly X is oxygen. More particularly R_6 is hydrogen or halogen when n is 1. More particularly A is C_1-C_6 alkylheterocyclyl when X is hydrogen and Y is



Unless otherwise noted, "alkyl" and "alkoxy" as used herein, whether used alone or as part of a substituent group, include straight and branched chains having 1 to 10 carbon atoms, or any number within this range. For example, alkyl radicals include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-butyl, *n*-pentyl, 3-(2-methyl)butyl, 2-pentyl, 2-methylbutyl, neopentyl, *n*-hexyl, 2-hexyl, 2-methylpentyl, and the like. Alkoxy radicals are oxygen ethers formed from the previously described straight or branched chain alkyl groups. Cycloalkyl groups contain 3 to 8 ring carbons and preferably 5 to 7 ring carbons. Similarly, alkenyl and alkynyl groups include straight and branched chain alkenes and alkynes having 1 to 10 carbon atoms, or any number within this range.

Unless otherwise stated, "aryl," employed alone or in combination with other terms (e.g., aryloxy, arylthioxy, arylalkyl), is an aromatic radical which can be a single

ring or multiple rings which are fused together or linked covalently. Illustrative aryl groups may be phenyl or naphthyl optionally substituted with one or more of the following: H, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, $COOR^1$, $CONR^1R^2$, OH, C_1-C_{10} alkyl ether, aryl or heterocyclyl ether, $OC(O)R^1$, $OC(O)OR^1$, $OC(O)NR^1R^2$, NR^1R^2, $NR^3C(O)R^1$, $NR^3C(O)OR^1$, $NR^3C(O)NR^1R^2$, halogen or halo (F, Cl, Br, I).

"Heterocyclyl" or "heterocycle" is a 3- to 8-member saturated or unsaturated heterocyclic group containing 1-4 nitrogens, an oxygen, or a sulfur atom; or one nitrogen and either oxygen or sulfur.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art as well as those methods set forth herein.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The term "subject" as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

Methods are known in the art for determining therapeutically and prophylactically effective doses for the instant pharmaceutical composition. The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

The term "prophylactically effective amount" refers to that amount of active compound or pharmaceutical agent that inhibits in a subject the onset of a disorder as being sought by a researcher, veterinarian, medical doctor or other clinician, the delaying of which disorder is mediated by the modulation of PPARγ activity.

Depending upon the biological environment (e.g., cell type, pathological condition of the host, etc.), these compounds can activate or block the actions of PPARγ. The utility of the compounds to treat disorders associated with Peroxisome Proliferator Activated Receptor gamma activity can be determined according to the procedures described herein. The present invention therefore provides a method of treating disorders associated with Peroxisome Proliferator Activated Receptor gamma activity in a subject in need thereof which comprises administering any of the compounds as defined herein in a quantity effective to treat such disorders. The compound may be administered to a patient by any conventional route of administration,

including, but not limited to, intravenous, oral, subcutaneous, intramuscular, intradermal and parenteral.

The present invention also provides pharmaceutical compositions comprising one or more compounds of this invention in association with a pharmaceutically acceptable carrier. The pharmaceutical composition may contain between about 0.1 mg and 1000 mg, preferably about 100 to 500 mg, of the compound, and may be constituted into any form suitable for the mode of administration selected. Carriers include necessary and inert pharmaceutical excipients, including, but not limited to, binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings. Compositions suitable for oral administration include solid forms, such as pills, tablets, caplets, capsules (each including immediate release, timed release and sustained release formulations), granules, and powders, and liquid forms, such as solutions, syrups, elixirs, emulsions, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions and suspensions.

To prepare the pharmaceutical compositions of this invention, one or more compounds of Formula I or salt thereof of the invention as the active ingredient, is intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral such as intramuscular. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example,

suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules, caplets, gelcaps and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, an amount of the active ingredient necessary to deliver an effective dose as described above. The pharmaceutical compositions herein will contain, per unit dosage unit, e.g., tablet, capsule, powder, injection, suppository, teaspoonful and the like, from about 0.01 mg to 30 mg/kg of body weight per day. Preferably, the range is from about 0.03 to about 15 mg/kg of body weight per day, most preferably, from about 0.05 to about 10 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 2 times per day. The dosages, however, may be varied depending upon the requirement of the patients, the severity of the condition being treated and the compound being employed. The use of

either daily administration or post-periodic dosing may be employed.

Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories; for oral parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. Alternatively, the composition may be presented in a form suitable for once-weekly or once-monthly administration; for example, an insoluble salt of the active compound, such as the decanoate salt, may be adapted to provide a depot preparation for intramuscular injection. For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the

advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include, aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions, include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin. The liquid forms in suitably flavored suspending or dispersing agents may also include the synthetic and natural gums, for example, tragacanth, acacia, methyl-cellulose and the like. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservatives are employed when intravenous administration is desired.

Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily

dosage may be administered in divided doses of two, three or four times daily. Furthermore, compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders; lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include, without limitation, starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

The daily dosage of the products may be varied over a wide range from 1 to 1000 mg per adult human per day. For oral administration, the compositions are preferably provided in the form of tablets containing, 0.01,0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100, 150, 200, 250 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily

supplied at a dosage level of from about 0.01 mg/kg to about 30 mg/kg of body weight per day. Particularly, the range is from about 0.03 to about 15 mg/kg of body weight per day, and more particularly, from about 0.05 to about 10 mg/kg of body weight per day. The compounds may be administered on a regimen of 1 to 2 times per day.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular compound used, the mode of administration, the strength of the preparation, the mode of administration, and the advancement of the disease condition. In addition, factors associated with the particular patient being treated, including patient age, weight, diet and time of administration, will result in the need to adjust dosages.

The compound of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of lipids, including but not limited to amphipathic lipids such as phosphatidylcholines, sphingomyelins, phosphatidylethanolamines, phophatidylcholines, cardiolipins, phosphatidylserines, phosphatidylglycerols, phosphatidic acids, phosphatidylinositols, diacyl trimethylammonium propanes, diacyl dimethylammonium propanes, and stearylamine, neutral lipids such as triglycerides, and combinations thereof. They may either contain cholesterol or may be cholesterol-free.

From Formula I it is evident that some of the compounds of the invention may have one or more asymmetric carbon atoms in their structure. It is intended that the

present invention includes within its scope the stereochemically pure isomeric forms of the compounds as well as their racemates. Stereochemically pure isomeric forms may be obtained by the application of art known principles. Diastereoisomers may be separated by physical separation methods such as fractional crystallization and chromatographic techniques, and enantiomers may be separated from each other by the selective crystallization of the diastereomeric salts with optically active acids or bases or by chiral chromatography. Pure stereoisomers may also be prepared synthetically from appropriate stereochemically pure starting materials, or by using stereoselective reactions.

Some of the compounds of the present invention may have trans and cis isomers. In addition, where the processes for the preparation of the compounds according to the invention give rise to mixture of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared as a single stereoisomer or in racemic form as a mixture of some possible stereoisomers. The non-racemic forms may be obtained by either synthesis or resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation. The compounds may also be resolved by covalent linkage to a chiral auxiliary, followed by chromatographic separation and/or crystallographic separation, and removal of the chiral auxiliary. Alternatively, the compounds may be resolved using chiral chromatography. The scope of the present invention is intended to cover all such isomers or stereoisomers per se, as well as mixtures of cis and trans

isomers, mixtures of diastereomers and racemic mixtures of enantiomers (optical isomers) as well.

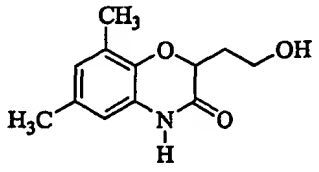
The chemistry of preparing compounds of Formula I is described in detail in U.S. Pat. Nos. 5,696,117 and 5,854,242, both to Frechette et al., and WO 97/17333 (Frechette et al.), all of which are hereby incorporated by reference in their entirety.

This invention will be better understood by reference to the examples that follow, but those skilled in the art will readily appreciate that these are only illustrative of the invention as described more fully in the claims which follow thereafter.

The following examples are intended to illustrate the invention but not to limit it.

Example 1

6,8-Dimethyl-2-(2-hydroxyethyl)-4*H*-benzo[1,4]oxazin-3-one

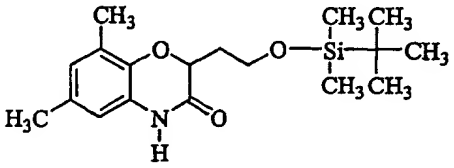


A solution of 2-amino-4,6-dimethylphenol (4.1 g, 30 mmol) in 40 mL of anhydrous DMF (N,N-dimethylformamide), under N_2, was cooled to 0 °C. Sodium hydride (75% dispersion in oil, 1.15 g, 36 mmol) was added in one portion, and the solution was stirred for 30 minutes at 0

°C. α-Bromo-γ-butyrolactone (3 mL, 36 mmol) was added dropwise *via* syringe, and the solution was heated to 70 °C for 18 h. The solution was cooled to room temperature, poured into 300 mL ice water, and stirred 30 minutes. The aqueous mixture was washed with 4 X 60 mL of 2:1 ethyl acetate/diethyl ether. The combined organic extracts were washed with 4 X 30 mL 1 N HCl, 4 X 30 mL water, and 30 mL brine. The organic phase was dried (Na_2SO_4), filtered, and solvent was removed *in vacuo*. Obtain 5.52 g (24.9 mmol).

Example 2

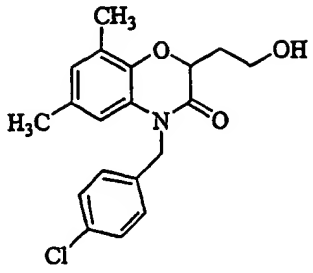
2-(2-*tert*-Butyldimethylsiloxyethyl)6,8-dimethyl-4*H*-benzo[1,4]oxazin-3-one



A solution of 2-(2-*tert*-Butyldimethylsiloxyethyl)6,8-dimethyl-4*H*-benzo[1,4]oxazin-3-one (5.5 g, 24.8 mmol) in 30 mL of anhydrous DMF, under N_2, was cooled to 0 °C. Imidazole (4.2 g, 62 mmol) was added in one portion, followed by addition of *tert*-butyldimethylsilyl chloride (5.6 g, 37.3 mmol) in one portion. The mixture was stirred 15 h as the ice bath thawed to room temperature. The reaction was poured into 300 mL water and washed with 4 X 50 mL of 7:3 diethyl ether/dichloromethane. The combined organics were washed with 4 X 30 mL water and 30 mL brine. The organics were dried (Na_2SO_4), filtered, and solvent was removed *in vacuo*. The product was isolated by silica gel chromatography with hexane/ethyl acetate. Obtain 7.0 g (20.9 mmol). Calcd for $C_{18}H_{29}NO_3Si$: C, 64.44; H, 8.71; N, 4.17. Found: C, 64.49; H, 8.61; N, 4.12.

Example 3

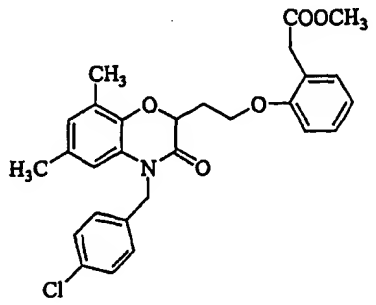
4-(4-Chlorobenzyl)-6,8-dimethyl-2-(2-hydroxyethyl)-4*H*-benzo[1,4]oxazin-3-one



A solution of 2-(2-*tert*-Butyldimethylsiloxyethyl)6,8-dimethyl-4*H*-benzo[1,4]oxazin-3-one (1.0 g, 2.98 mmol) in 40 mL anhydrous DMF, under N_2, was cooled to 0 °C. Sodium hydride (75% dispersion in oil, 0.115 g, 3.58 mmol) was added in one portion and the solution was stirred for 40 min at 0 °C. The ice bath was removed, 4-chlorobenzyl chloride (0.483 g, 3.0 mmol) was added and the solution was stirred at room temperature for 15 h. The mixture was poured into 200 mL ice water, salt was added, and stirring continued for 20 min. The aqueous mixture was washed with 4 X 50 mL diethyl ether. The combined organic were washed with 4 X 30 mL water and 30 mL brine. The organics were dried (Na_2SO_4), filtered, and solvent was removed *in vacuo*. The product was dissolved in 20 mL methanol and 0.5 mL water. Three drops of methanesulfonic acid were added and the mixture was stirred at room temperature for two hours. Solvent was removed *in vacuo* and the product was isolated by silica gel chromatography with hexane/ethyl acetate. Obtain 0.685 g (1.98 mmol). Calcd for $C_{19}H_{20}ClNO_3$: C, 65.99; H, 5.83; N, 4.05. Found: C, 65.91; H, 5.87; N, 3.95.

Example 4

Methyl 2-(2-(4-(4-chlorobenzyl)-6,8-dimethyl-4*H*-benzo[1,4]oxazin-3-one-2-yl)ethoxy)phenylacetate



A solution of 4-(4-chlorobenzyl)-6,8-dimethyl-2-(2-hydroxyethyl)-4*H*-benzo[1,4]oxazin-3-one (0.648 g, 1.87 mmol), (2-hydroxyphenyl)acetic acid (0.467 g, 2.81 mmol), and tributylphosphine (0.7 mL, 2.81 mmol) in 50 mL anhydrous benzene, under N_2, was cooled to 10 °C. 1,1'-(Azodicarbonyl)dipiperidine (0.708 g, 2.81 mmol) was added in one portion, and the solution was stirred at 55 °C for 17 h. The solution was washed with 4 X 10 mL 1 N NaOH, 2 X 20 mL water, and 20 mL brine. The organics were dried (Na_2SO_4), filtered, and solvent was removed *in vacuo*. The product was purified by silica gel chromatography with hexane/ethyl acetate. Obtain 175 mg (0.35 mmol). Anal. Calcd for $C_{28}H_{28}ClNO_5$: C, 68.08; H, 5.71; N, 2.84. Found: C, 68.29; H, 5.69; N, 2.69.

Example 5

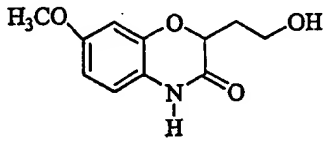
2-(2-(4-(4-Chlorobenzyl)-6,8-dimethyl-4*H*-benzo[1,4]oxazin-3-one-2-yl)ethoxy)phenylacetic acid

To a solution of methyl 2-(2-(4-(4-chlorobenzyl)-6,8-dimethyl-4*H*-benzo[1,4]oxazin-3-one-2-yl)ethoxy)phenylacetate (0.165 g, 0.33 mmol) in 10 mL methanol was added 2 mL 2 N NaOH. The solution was

stirred at 50 °C for three h open to air, the cooled to 0 °C. The solution was diluted with 10 mL water, acidified with 0.5 mL conc. HCl (6 mmol), and extracted with 4 X 10 mL dichloromethane. The combined organics were washed with 15 mL water and 20 mL 1:1 water/brine, dried (Na_2SO_4), and filtered. Solvent was removed *in vacuo* to the title compound. Obtain 136 mg (0.28 mmol). Anal. Calcd. for $C_{27}H_{26}ClNO_5$: C, 67.57; H, 5.46; N, 2.92. Found: C, 67.26; H, 5.44; N, 2.72.

Example 6

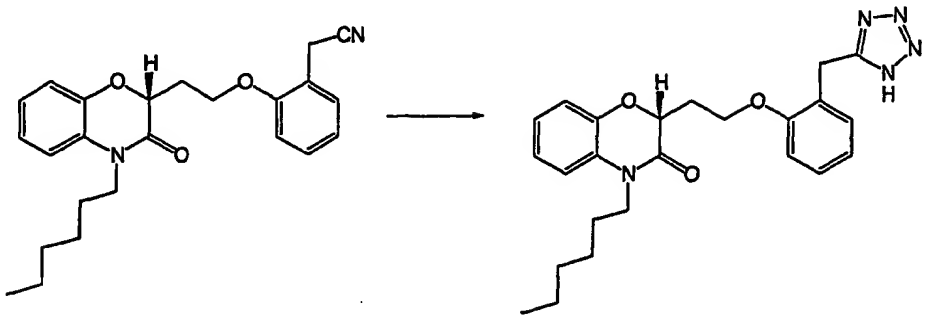
2-(2-Hydroxyethyl)-7-methoxy-4*H*-benzo[1,4]oxazin-3-one



A solution of 5-methoxy-2-nitrophenol (2.4 g, 13.2 mmol) in 50 mL anhydrous DMF, under N_2, was cooled to 0 °C. Potassium carbonate (2.4 g, 17.2 mmol) was added, followed by dropwise addition of α-bromo-γ-butyrolactone (1.3 mL, 15.8 mmol). The reaction was stirred at room temperature for 17 h. Acetic acid (1.5 mL) was added, the mixture was poured into 300 mL water, and the intermediate was obtained as a solid by filtration. The intermediate (3.37 g, 13.3 mmol) was suspended in 75 mL ethyl acetate and 50 mL ethanol, then shaken for six h with 10 % Pd/C and H_2 (45 psi) at room temperature. The solution was filtered through Celite and solvent was removed *in vacuo*. Obtain 2.97 g (13.3 mmol). Anal. Calcd. For $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.27. Found: C, 59.07; H, 5.72; N, 6.27.

Example 7

2*H*-1,4-Benzoxazin-3(4*H*)-one, 4-hexyl-2-[2-[2-(1*H*-tetrazol-5-ylmethyl)phenoxy]ethyl]-, (2*R*)-



As shown in the above scheme, to a solution of the nitrile (540 mg, 1.38 mmol) in toluene (3 mL) was added sodium azide (116 mg, 1.79 mmol) and triethylamine hydrochloride (246 mg, 1.79 mmol). The reaction was heated at 100 °C for 20 h. The mixture was diluted with water and ethyl acetate (10 mL each) and acidified to pH=1 with conc. hydrochloric acid. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give 122 mg of the tetrazole as a white solid. MS: 458 (M+Na)

aP2 Assay for Antagonist

Twenty-four hours after the initial seeding of the 96-well plates by hand (around 20,000/well), the differentiation assay may be initiated. Medium may be removed and replaced with 150µl of differentiation medium containing vehicle (DMSO) or test compounds with a known aP2 activator or such aP2 activator alone. Cells may be returned to incubator for 24 hours culture. At the termination of the challenge, medium may be removed and 100 µl of lysis buffer may be added to initiate the bDNA

aP2 mRNA assay. The branched DNA assay may be performed according to the manufacturer's protocol (Bayer Diagnostics; Emeryville, CA). Result may be expressed as percent inhibition of aP2 mRNA production activated by the aP2 activator. IC_{50}'s may be determined by non-linear regression with a sigmoidal fit curve.

Following the challenge of the preadipocytes, cells may be lysed with lysis buffer (Bayer Diagnostics) containing the aP2 oligonucleotides. After a 15 minutes incubation at 53°C or 30 minutes at 37°C incubator, 70 µl of the lysis buffer from each well may be added to a corresponding capture well (preincubated with 70 µl of blocking buffer (Bayer Diagnostics)). The capture plate may be incubated overnight at 53°C in a plate incubator (Bayer Diagnostics). After this incubation, the bDNA and labeled probes may be annealed as directed by the manufacturer. Following a 30-minute incubation with the luminescent alkaline phosphatase substrate, dioxitane, the luminescence may be quantitated in a Dynex MLX microtiter plate luminometer. Oligonucleotide probes designed to anneal to the aP2 mRNA and function in the bDNA mRNA detection system are designed with *ProbeDesigner* software (Bayer Diagnostics). This software package analyzes a target sequence of interest with a series of algorithms in order to determine which regions of the sequence can perform as locations for capture, label, or spacer probe annealing. The sequences of the oligonucleotides are as follows:

SEQ ID NO.1 CATTTTGTGAGTTTTCTAGGATTATTCTTTTCTCTTGGAAAGAAAGT
SEQ ID NO.2 ATGTTAGGTTTGGCCATGCCTTTCTCTTGGAAAGAAAGT
SEQ ID NO.3 CCTCTCGTTTTCTCTTTATGGTTTTCTCTTGGAAAGAAAGT
SEQ ID NO.4 GCTTATGCTCTCTCATAAACTCTCGTGGTTTCTCTTGGAAAGAAAGT

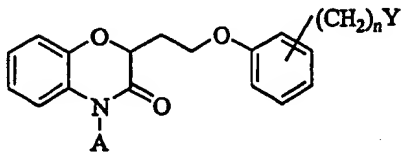
SEQ ID NO.5 CCAGGTACCTACAAAAGCATCACATTTAGGCATAGGACCCGTGTCT
SEQ ID NO.6 GCCCACTCCTACTTCTTTCATATAATCATTTAGGCATAGGACCCGTGTCT
SEQ ID NO.7 AGCCACTTTCCTGGTGGCAAATTTAGGCATAGGACCCGTGTCT
SEQ ID NO.8 CATCCCCATTCACACTGATGATCTTTAGGCATAGGACCCGTGTCT
SEQ ID NO.9 GTACCAGGACACCCCCATCTAAGGTTTTTAGGCATAGGACCCGTGTCT
SEQ ID NO.10 GGTTGATTTTCCATCCCATTTCTGCACATTTTAGGCATAGGACCCGTGTCT
SEQ ID NO.11 GCATTCCACCACCAGTTTATCATTTTAGGCATAGGACCCGTGTCT
SEQ ID NO.12 GCGAACTTCAGTCCAGGTCAACGTCCCTTGTTTAGGCATAGGACCCGTGTCT
SEQ ID NO.13 TCCCACAGAATGTTGTAGAGTTCAATTTTAGGCATAGGACCCGTGTCT
SEQ ID NO.14 AAAACAACAATATCTTTTTGAACAATATATTTAGGCATAGGACCCGTGTCT
SEQ ID NO.15 TCAAAGTTTTCACTGGAGACAAGTTT
SEQ ID NO.16 AAAGGTACTTTCAGATTTAATGGTGATCA
SEQ ID NO.17 CTGGCCCAGTATGAAGGAAATCTCAGTATTTTT
SEQ ID NO.18 TCTGCAGTGACTTCGTCAAATTC
SEQ ID NO.19 ATGGTGCTCTTGACTTTCCTGTCA
SEQ ID NO.20 AAGTGACGCCTTTCATGAC

aP2 Assay for Agonist

The procedure is described in detail in Burris *et al.*, *Molecular Endocrinology*, 1999, 13:410, which is hereby incorporated by reference, and aP2 assay results of agonist intrinsic activity may be presented as fold increase over vehicle in induction of aP2 mRNA production. Tables 1-3 below set forth the mass spectra data and the agonist intrinsic activity of some compounds of the present invention.

Table 1

Compounds of this invention wherein Z_1 and Z_2 are both H



Compound No.	A	Pos (n) Y	MS (MH^+/M+Na)	Agonist Intrinsic Activity
1	4-MeOBn	2(1) $COOCH_3$	462	1.1
2	4-MeOBn	2(1) COOH	448	20.8
3	3-MeOBn	2(1) $COOCH_3$	462	1.2
4	3-MeOBn	2(1) COOH	448	24.1
5	4-MeOPhCH_2CH_2	2(1) $COOCH_3$	476	1.8
6	4-MeOPhCH_2CH_2	2(1) COOH	462	26.2
7	3,5-$(MeO)_2$Bn	2(1) $COOCH_3$	492	2.0
8	3,5-$(MeO)_2$Bn	2(1) COOH	478	15.4
9	3,4-(OCH_2O)Bn	2(1) $COOCH_3$	476	1.3
10	3,4-(OCH_2O)Bn	2(1) COOH	462	27.4
11	4-MeBn	2(0) COOH	418	3.9
12	4-MeBn	2(1) $COOCH_3$	446	1.0
13	4-MeBn	2(1) COOH	432	16.3
14	4-MeBn	2(2) $COOCH_3$	460	1.0
15	4-MeBn	2(2) COOH	446	4.4
16	4-MeBn	3(1) $COOCH_3$	446	0.9
17	4-MeBn	3(1) COOH	432	8.1
18	4-MeBn	3(2) $COOCH_3$	460	1.0
19	4-MeBn	3(2) COOH	446	7.1
20	3-MeBn	2(0) COOH	418	4.4
21	3-MeBn	2(1) $COOCH_3$	446	0.8
22	3-MeBn	2(1) COOH	432	23
23	3-MeBn	2(2) $COOCH_3$	460	1.0
24	3-MeBn	2(2) COOH	446	8.4
25	3-MeBn	2(3) $COOCH_3$	474	1.3
26	3-MeBn	2(3) COOH	460	10.2
27	3-MeBn	3(1) $COOCH_3$	446	1.0
28	3-MeBn	3(1) COOH	432	8.2
29	3-MeBn	3(2) $COOCH_3$	460	1.0
30	3-MeBn	3(2) COOH	446	14.7
31	Bn	2(0) COOH	404	4.0
32	Bn	2(1) $COOCH_3$	432	1.2
33	Bn	2(1) COOH	418	18.1
34	Bn	3(1) $COOCH_3$	432	0.9
35	Bn	3(1) COOH	418	11.0
36	4-ClBn	2(0) COOH	438	3.5

37	4-ClBn	2(1)$COOCH_3$	466	0.9
38	4-ClBn	2(1)COOH	452	16.6
39	4-ClBn	2(2)$COOCH_3$	480	0.9
40	4-ClBn	2(2)COOH	466	2.6
41	4-ClBn	2(3)$COOCH_3$	494	1.0
42	4-ClBn	2(3)COOH	480	2.9
43	4-ClBn	3(1)$COOCH_3$	466	4.5
44	4-ClBn	3(1)COOH	452	13.1
45	4-ClBn	3(2)$COOCH_3$	480	3.5
46	4-ClBn	3(2)COOH	466	4.2
47	3-ClBn	2(0)COOH	438	4.9
48	3-ClBn	2(1)$COOCH_3$	466	0.8
49	3-ClBn	2(1)COOH	452	6.2
50	3-ClBn	2(2)$COOCH_3$	480	-
51	3-ClBn	2(2)COOH	466	-
52	3-ClBn	2(3)$COOCH_3$	494	-
53	3-ClBn	2(3)COOH	480	8.4
54	3-ClBn	3(1)$COOCH_3$	466	-
55	3-ClBn	3(1)COOH	452	5.5
56	3-ClBn	3(2)$COOCH_3$	480	-
57	3-ClBn	3(2)COOH	466	5.6
58	2-ClBn	2(1)$COOCH_3$	466	1.0
59	2-ClBn	2(1)COOH	452	10.4
60	2-ClBn	3(1)$COOCH_3$	466	0.9
61	2-ClBn	3(1)COOH	452	7.3
62	3,5-Cl_2Bn	2(0)COOH	472	-
63	3,5-Cl_2Bn	2(1)$COOCH_3$	500	-
64	3,5-Cl_2Bn	2(1)COOH	486	29.0
65	3,5-Cl_2Bn	2(2)$COOCH_3$	514	-
66	3,5-Cl_2Bn	2(2)COOH	500	4.2
67	3,5-Cl_2Bn	2(3)$COOCH_3$	528	-
68	3,5-Cl_2Bn	2(3)COOH	514	5.7
69	3,5-Cl_2Bn	3(1)$COOCH_3$	500	-
70	3,5-Cl_2Bn	3(1)COOH	486	6.2
71	3,5-Cl_2Bn	3(2)$COOCH_3$	514	-
72	3,5-Cl_2Bn	3(2)COOH	500	6.3
73	2,4-Cl_2Bn	2(1)$COOCH_3$	500	0.6
74	2,4-Cl_2Bn	2(1)COOH	486	16.9
75	3,4-Cl_2Bn	2(1)$COOCH_3$	500	0.9
76	3,4-Cl_2Bn	2(1)COOH	486	30.8
77	3,4-$Cl_2PhCH_2CH_2$	2(1)$COOCH_3$	514	-
78	3,4-$Cl_2PhCH_2CH_2$	2(1)COOH	500	35.9
79	4-BrBn	2(1)$COOCH_3$	510	1.3
80	4-BrBn	2(1)COOH	496	29.5
81	4-FBn	2(1)$COOCH_3$	450	0.8
82	4-FBn	2(1)COOH	436	22.0
83	3,4-F_2Bn	2(1)$COOCH_3$	468	1.3
84	3,4-F_2Bn	2(1)COOH	454	20.0

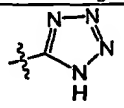
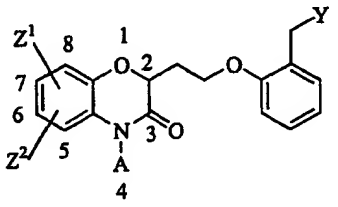
85	Me	2(1) $COOCH_3$	356	1.2
86	Me	2(1) COOH	342	6.5
87	Et	2(1) $COOCH_3$	370	3.8
88	Et	2(1) COOH	356	14.4
89	n-Pr	2(1) $COOCH_3$	384	3.9
90	n-Pr	2(1) COOH	370	28.9
91	i-Pr	2(1) $COOCH_3$	384	1.3
92	i-Pr	2(1) COOH	370	8.6
93	n-Bu	2(1) $COOCH_3$	398	2.8
94	n-Bu	2(1) COOH	384	15.8
95	i-Bu	2(1) $COOCH_3$	398	1.8
96	i-Bu	2(1) COOH	384	22.4
97	n-Pent	2(1) $COOCH_3$	412	1.7
98	n-Pent	2(1) COOH	398	33.6
99	n-Hex	2(1) $COOCH_3$	426	1.1
100	n-Hex	2(1) 	458 (M+ Na)	14.37

Table 2

Compounds of this invention where Z_1 and Z_2 are not both H



Compound No.	Z_1 / Z_2	A	Y	MS (MH$^+$/M+ Na)	Agonist Intrinsic Activity
101	5-Me	3,4-Cl_2Bn	$COOCH_3$	515	2.3
102	5-Me	3,4-Cl_2Bn	COOH	500	26.4
103	5-Me	4-MeOBn	$COOCH_3$	476	2.5
104	5-Me	4-MeOBn	COOH	462	9.3
105	6-Me	4-ClBn	$COOCH_3$	480	1.0
106	6-Me	4-ClBn	COOH	466	-
107	7-Me	4-ClBn	$COOCH_3$	480	1.4
108	7-Me	4-ClBn	COOH	466	32.7
109	6,8-Me_2	4-ClBn	$COOCH_3$	494	-
110	6,8-Me_2	4-ClBn	COOH	480	7.3
111	6-Cl	4-ClBn	$COOCH_3$	501	1.9

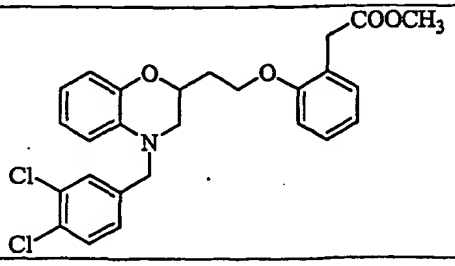
112	6-Cl	4-ClBn	COOH	486	9.9
113	6,8-Cl_2-7-Me	4-ClBn	$COOCH_3$	549	-
114	6,8-Cl_2-7-Me	4-ClBn	COOH	534	1.1
115	6-Ac	4-ClBn	$COOCH_3$	508	0.6
116	6-Ac	4-ClBn	COOH	494	17.8
117	7-MeO	4-ClBn	$COOCH_3$	496	0.9
118	7-MeO	4-ClBn	COOH	482	18.5
119	6,7-CH=CH-CH=CH	4-ClBn	$COOCH_3$	516	0.7
120	6,7-CH=CH-CH=CH	4-ClBn	COOH	502	7.1
121	6-Ph	4-ClBn	$COOCH_3$	543	0.7
122	6-Ph	4-ClBn	COOH	529	4.4
123	6-Me-7-Ph	4-ClBn	$COOCH_3$	557	0.9
124	6-Me-7-Ph	4-ClBn	COOH	543	23.2
125	6-Me-7-Ph	Hex	$COOCH_3$	516	2.2
126	6-Me-7-Ph	Hex	COOH	502	23.3
127	7-COOMe	4-ClBn	$COOCH_3$	524	1.6
128	7-COOH	4-ClBn	COOH	496	1.1
129	7-COOMe	4-ClBn	COOH	510	27.1
130	6-F	4-ClBn	$COOCH_3$	484	1.2
131	6-F	4-ClBn	COOH	470	6.0
132	6-F	Hex	$COOCH_3$	444	0.8
133	6-F	Hex	COOH	430	6.2
134	7-COOMe	Hex	COOH	492 (M+ Na)	49.3

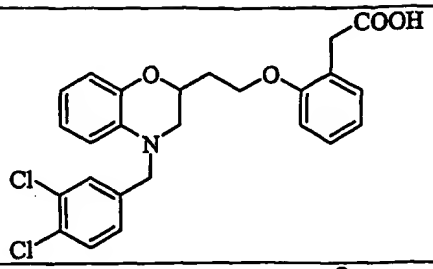
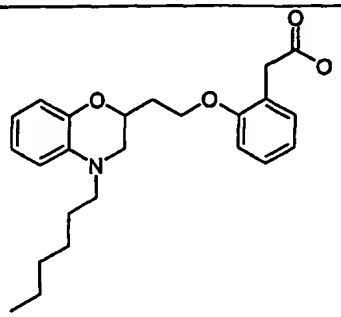
Keys:

Me=methyl; Et=ethyl; Pr=propyl; Bu=butyl;
Pent=pentyl; Hex=hexyl; Ac=acetyl; Bn=benzyl.

Table 3

Reduced amines of this invention

Compound No.	Structure	MS (MH^+)	Agonist Intrinsic Activity
135		487	0.9

136		473	47.4
137		398	40.33

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

SEQUENCE LISTING

<110> Rybczynski, Philip
et al.

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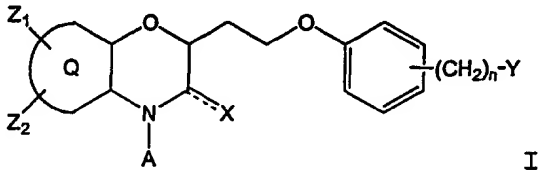
WHAT IS CLAIMED IS:

1. A method of treating a subject suffering from a condition associated with Peroxisome Proliferator Activated Receptor gamma activity, which comprises administering to said subject an effective amount of a compound of Formula (I),



I

or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, ester, prodrug form, or a pharmaceutically acceptable salt thereof, wherein

Q is a fused phenyl or fused pyridyl moiety;

Z_1 is hydrogen, halogen, $COOR_1$, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl;

Z_2 is hydrogen or a halogen;

X is hydrogen or oxygen;

A is C_1-C_6 alkyl, C_1-C_6 alkylaryl or C_1-C_6 alkylheterocyclyl

wherein said aryl is biphenyl, naphthyl or phenyl; and said heterocyclyl is a 5- or 6-membered saturated or unsaturated heterocyclic group containing 1-4 nitrogen atoms, an oxygen or sulfur atom;

wherein said aryl or heterocyclyl group is optionally substituted with C_1-C_6 alkyl, benzyl, oxybenzyl, phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro,

amino, carboxyl, carbo(C_1-C_6)alkoxy, or methylsulfonylamino;

n is an integer from 0-3; and

Y is selected from

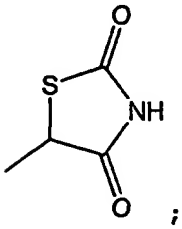
(a) NHR_1R_2, $N^+R_1R_2R_3$;

(b) $NHC(NR_4)NR_5$;

(c) CO_2H, CHO;

(d) $CH(R_6)COOH$, $CH(R_6)COOCH_3$, $CH=CHR_7$, $CH=C(COOH)_2$;

(e) a moiety of the formula



;

(f) 5-tetrazolyl,

wherein

R_1, R_2 and R_3 are independently hydrogen, C_1-C_6 alkyl, or t-butoxycarbonyl;

R_4 and R_5 are independently t-butoxycarbonyl or hydrogen, or R_4 and R_5 may be joined together to form an imidazoline, imidazolyl or pyrimidine ring;

R_6 is hydrogen, hydroxy, or halogen; and

R_7 is CO_2H or $C(O)NH(CH_2)_pOH$ wherein p is an integer from 1-4.

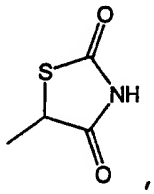
2. A method of Claim 1 wherein said condition is reduced insulin sensitivity.

3. A method of Claim 1 wherein said condition is selected from Non-Insulin Dependant Diabetes Mellitus, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis polycystic ovary syndrome, hypertension, ischemia, stroke,

heart disease, irritable bowel disorder, inflammation, and cataract.

4. A method of Claim 3 wherein said condition is Non-Insulin Dependant Diabetes Mellitus.

5. A method of Claim 1 wherein Y is selected from CO_2H, CHO, $CH(R_6)COOH$, $CH(R_6)COOCH_3$, $CH=CHR_7$, $CH=C(COOH)_2$, a moiety of the formula

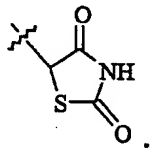


, and 5-tetrazolyl, wherein R_6 and R_7 are as claimed in Claim 1.

6. A method of Claim 1 wherein R_6 is hydrogen or halogen when n is 1.

7. A method of Claim 6 wherein X is oxygen.

8. A method of Claim 6 wherein A is C_1-C_6 alkylheterocyclyl when X is hydrogen and Y is



.

9. A method of Claim 6 wherein Y is $COOCH_3$ or COOH.

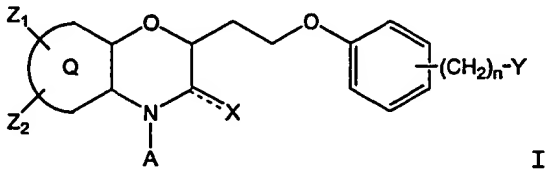
10. A method of Claim 9 wherein said condition is selected from Non-Insulin Dependant Diabetes Mellitus, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis polycystic ovary syndrome, hypertension, ischemia, stroke,

heart disease, irritable bowel disorder, inflammation, and cataract.

11.A method of Claim 10 wherein said condition is Non-Insulin Dependant Diabetes Mellitus.

12.A method of Claim 10 wherein said condition is obesity.

13.A method of inhibiting in a subject the onset of a condition associated with Peroxisome Proliferator Activated Receptor gamma activity, which comprises administering to the subject a prophylactically effective dose of a compound of Formula (I),



I

or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, ester, prodrug form, or a pharmaceutically acceptable salt thereof, wherein

Q is a fused phenyl or fused pyridyl moiety;

Z_1 is hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, phenyl, hydroxy, amino, nitro, sulfonylamino or trifluoromethyl;

Z_2 is hydrogen or a halogen;

X is hydrogen or oxygen;

A is C_1-C_6 alkyl, C_1-C_6 alkylaryl or C_1-C_6 alkylheterocyclyl

wherein said aryl is biphenyl, naphthyl or phenyl; and said heterocyclyl is a 5- or 6-membered saturated or

unsaturated heterocyclic group containing 1-4 nitrogen atoms, an oxygen or sulfur atom;

wherein said aryl or heterocyclyl group is optionally substituted with C_1-C_6 alkyl, benzyl, oxybenzyl, phenoxy, hydroxy, alkoxy, halogen, dihalogen, nitro, amino, carboxyl, carbo(C_1-C_6)alkoxy, or methylsulfonylamino;

n is an integer from 0-3; and

Y is selected from

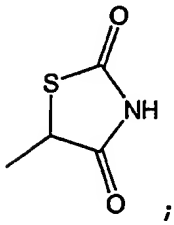
(a) NHR_1R_2, $N^+R_1R_2R_3$;

(b) $NHC(NR_4)NR_5$;

(c) CO_2H, CHO;

(d) $CH(R_6)COOH$, $CH(R_6)COOCH_3$, $CH=CHR_7$, $CH=C(COOH)_2$;

(e) a moiety of the formula



;

(f) 5-tetrazolyl,

wherein

R_1, R_2 and R_3 are independently hydrogen, C_1-C_6 alkyl, or t-butoxycarbonyl;

R_4 and R_5 are independently t-butoxycarbonyl or hydrogen, or R_4 and R_5 may be joined together to form an imidazoline, imidazolyl or pyrimidine ring;

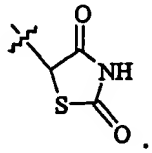
R_6 is hydrogen, hydroxy, or halogen; and

R_7 is CO_2H or $C(O)NH(CH_2)_pOH$ wherein p is an integer from 1-4.

14. A method of Claim 13 wherein R_6 is hydrogen or halogen when n is 1.

15. A method of Claim 14 wherein X is oxygen.

16. A method of Claim 14 wherein A is C_1-C_6 alkylheterocyclyl when X is hydrogen and Y is



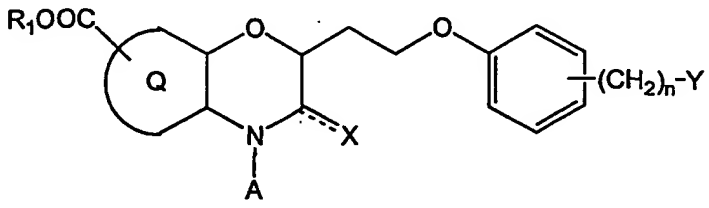
17.A method of Claim 16 wherein said condition is reduced insulin sensitivity.

18. A method of Claim 16 wherein said condition is selected from Non-Insulin Dependant Diabetes Mellitus, obesity, nephropathy, neuropathy, retinopathy, atherosclerosis polycystic ovary syndrome, hypertension, ischemia, stroke, heart disease, irritable bowel disorder, inflammation, and cataract.

19.A method of Claim 18 wherein said condition is Non-Insulin Dependant Diabetes Mellitus.

20.A method of Claim 18 wherein said condition is obesity.

21. A compound of Formula (Ia):



Ia

or an optical isomer, enantiomer, diastereomer, racemate or racemic mixture thereof, ester, prodrug form, or a

pharmaceutically acceptable salt thereof, wherein A, Q, X, Y, R_1, and n are as claimed in claim 1.